REMARKS

The present amendment is in response to the Office Action dated January 6, 2006. A two-month extension of time for response is requested and the Patent Office is authorized to charge the underpayment to Deposit Account No. 01-2300 for the appropriate extension fees that are included with the response.

Claims 1-53 are pending in the present application. Claims 1-26 have been examined, while Claims 27-53 are withdrawn from consideration at this time, pursuant to a restriction requirement.

Applicants hereby cancel Claims 27-53, but expressly reserve the right to refile the subject matter of these claims in a further divisional application. Applicants have also amended Claims 6, 7, 15, 16, 20, 21 and 25 to further define the present invention.

Applicants request that the substitute specification filed December 27, 2001 be entered in the present case. Pursuant to 37 CFR 1.125(b), the substitute specification contains no new matter.

Applicants have amended the first paragraph of the specification to update the history of the parent applications to the present application, including correcting the serial number of the provisional patent application filed December 15, 1995 from 60/008,317 to 60/008,717. Applicants made a typographical error in the serial number of the listed provisional in the present application. Support for this correction may be found by reviewing the priority data for the parental applications/patents. Also, a copy of the filing receipt of the parent application serial number 08/766,354 filed on December 13, 1996 (now U.S. Patent No. 6,013,487), which claims benefit to provisional application number

60/008,717 filed on December 15, 1995, showing the correct serial number and filing date is enclosed.

The Examiner has stated that the applicants have provided an incorrect priority date for the present application. As noted in the preceding paragraph, the listed provisional application contained a typographical error. Serial Number 10/008,717 (the correct application) was filed December 15, 1995.

ENABLEMENT REJECTION

Claims 10-26 have been rejected under 35 USC §112¶1 as lacking enablement. The Examiner has apparently erroneously focused her arguments on the invention being totally directed to gene therapy for cystic fibrosis (the subject of applicants' immediate parent case, now U.S. Patent No. 6,280,978). While the present invention does contemplate the use of RNA trans-splicing for correction of CFTR in cells of individuals with cystic fibrosis, this is only a portion of the present invention. In fact, only dependent claims 15 and 16 (cell) and 20, 21 and 25 (method of use) are directed to CFTR.

In fact, the present invention provides an improvement of applicants' RNA trans-splicing technology for correcting genetic defects in a target pre-mRNA molecule in a cell. Gene therapy for genetic diseases, such as cystic fibrosis, is only one potential use of the applicants' transplicing technology. While the Examiner cites to the priority application (December, 1995) and provides a news report from 1995 allegedly detailing the failure of gene therapy to bolster her non-enablement argument, applicants have already received three patents on the technology, all stemming from the original 1995 provisional application,

including one relating to cystic fibrosis and correction of a defective CFTR transcript. The present case is a continuation-in-part of the earlier cases.

As noted, the present invention is an improvement on the technology (dating from the CIP filing date – January 2001) wherein the pre-transplicing molecule (PTM) contains at least two target binding domains to improve trans-splicing efficacy. The Applicants' RNA trans-splicing technology has been routinely shown to work *in vivo* in model systems, see, e.g. Section 6.2.8 of present application – tumor killing in a thymic nude mice and targeting a diptitheria toxin RNA. As noted above, claims 10-26 are directed to cells containing and methods utilizing a PTM containing at least two target binding domains that target binding of the PTM to a target pre-mRNA in a cell for trans-splicing. Applicants have shown that this improvement – the use of at least two binding domains – improves the efficacy of the trans-splicing reaction.

However, since the Examiner has focused on cystic fibrosis in her arguments, Applicants specifically address this issue.

At a minimum, the immediate parent to the present application, now U.S. Patent No. 6,280,978, which deals with correction of cystic fibrosis by RNA trans-splicing (as here), was clearly found to be enabled. As noted, the present invention provides an improvement over applicants' prior patent by providing a PTM with multiple binding domains that more efficiently corrects a CFTR pre mRNA containing a mutation, such that a functional CFTR protein is produced. To say that the presently claimed invention lacks enablement whereas the parent case was clearly enabled is to have truly inconsistent prosecution. Moreover, the

Examiner has recognized the relatedness of the presently claimed invention to those of the parent cases by issuing double patenting rejections (see below).

As noted above, the Examiner's reliance on the 1995 *Science* news article is misplaced. To support the argument, the Examiner also relies on the 2005 publication by Tate et al. to show that gene therapy for cystic fibrosis is difficult. However, a careful reading of this reference shows a favorable view of the RNA trans-splicing technology of the present invention for correcting the CFTR defect (see page 275), as an alternative to gene therapy.

Claims 10-26 are directed to cells containing PTMS (having two or more binding domains and methods to provide a host cell with a chimeric mRNA molecule using the PTMs of the invention. The independent claims are not specifically directed to treatment of a particular disease, let alone cystic fibrosis. However, since this has been treated as a "gene therapy" rejection Applicants address this issue. The PTO has long taken the position that several considerations go into examination of "gene therapy" claims: sufficient administration, sufficient expression, art-recognized model, phenotypic change correlated to the disease (see, e.g. Deborah Reynolds, "Broadening the Scope of Gene Therapy Claims," presented at the PTO Biotechnology Customer Partnership, August 3, 2004, slides available at www.cabic.com/bcp/080304/Reynolds_BSGT.ppt).

Applicants have clearly shown all of the above-considerations. In addition, Applicants, together with several collaborators who work in CF therapy field, have published several articles, in accordance with the teachings of the present invention, where correction of the CFTR defect *in vivo* in an art-recognized CF model system has been

clearly demonstrated. See Liu et al., *Nature Biotechnology* 20:47-52 (2002); Liu et al., *Human Gene Therapy* 16:1116-1123 (2005), copies enclosed. Both papers use multi-binding domain (two or more) PTMs, as claimed, and show correction of the CTFR mediated chloride ion channel defect in CF airways. The results of the *Nature Biotechnology* paper showed that RNA trans-splicing using the PTMs of this present invention resulted in a 16-22% functional repair of the CF defect (8% correction is considered therapeutic). The PTMs were delivered with an adenoviral vector. The *Human Gene Therapy* paper provides an update of this work (using the same PTM technology of the present invention) with AAV as the delivery vector. AAV can be readily utilized here, because a full length CFTR gene is not required and the more readily packagable PTM may be utilized. Functional correction of the CF defect was clearly demonstrated in the art-recognized model.

In view of the remarks above, Applicants maintain that the rejection of Claims 10-26 for lack of enablement should be withdrawn.

WRITTEN DESCRIPTION REJECTION

Claims 1-26 have been rejected under 35 USC §112 1 as lacking an adequate written description. The Examiner alleges that the present application does not provide enough information to show that Applicants were in possession of the claimed invention.

In the present situation, the Examiner argues that there is insufficient structural information regarding the binding domains of the PTMs of the invention citing to the PTO guidelines on written description as to requiring an explicit recitation of structure to satisfy

written description. Again, the Examiner has erroneously focused on the binding domains targeted to a CFTR transcript, but Applicants will focus their remarks on CFTR, which exemplifies the presently claimed invention.

However, the remarks are equally applicable to the broader scope of the claims.

Several recent decisions of the Court of Appeals for the Federal Circuit have held that "there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." See *Falkner et al. v. Inglis et al.*, Slip. Op. (Fed.Cir., May 26, 2006), copy attached; See also, *Capon v. Eschar*, 418 F. 3d 1349, 76 U.S.P.Q. 1078 (Fed. Cir. 2005), copy attached. The *Falker* case dealt with written description for a modified pox virus having a deleted or inactivated gene. No specific genes were identified. The CAFC said that providing the structure of the genes was not required since they were well-known in the art. A similar rationale was applied in *Capon*, which dealt with chimeric antibody molecule genes. The court held that the sequence of the chimeric genes was not necessary, since they were well known in the art.

In the present case, the Examiner argues that applicants have not provided sufficient information regarding the binding domains for the CFTR gene. The Examiner has acknowledged that Applicants have provided several examples that target exon 9 in order to correct exon 10 which contains the most prevalent CFTR mutation, Δ508, e.g., PTM 30 and 24 (Figures 42 and 43). In addition, as set forth in the attached article, Puttaraju et al., *Molecular Therapy* 4:105-114 (2001), applicants contemporaneously with the filing of the present case constructed several additional PTMs containing at least two binding domains, in accordance with the teachings of the present invention that would repair the CFTR

mutant. See, in particular, Figure 1b and top of page 108. The same PTMs were used in the *in vivo* experiments described above in the *Nature Biotechnology* and *Human Gene Therapy* articles.

The Examiner has argued that despite the description of the specific PTMs in the specification, the skilled artisan would not be able to predict the actual structural description of the full scope of target binding domains that would target the PTMs of the invention to a CFTR pre MRNA (mammalian or otherwise) encompassed by the claims.

The Examiner is in error. CFTR is a well characterized protein (and so is the DNA encoding it) whose structure was well known in the art, prior to the invention. See, Welsh et al., Cystic Fibrosis, in Scriver et al., eds., *The Metabolic Basis of Inherited Disease*, 7th Ed., pp. 3799-3878 (1995), copy attached. This article sets forth a detailed description of CFTR as well as the structure of the many mutations in the DNA encoding CFTR that can give rise to cystic fibrosis. The most prevalent mutation that causes CF is the Δ508 mutation.

Like *Capon* and *Falker*, Applicants do not have to recite a structure for every possible binding domain to satisfy the written description requirement. It is well within the skill of the practitioner to readily predict the structure of a binding domain for CFTR, since it is such a well-characterized molecule whose structure (including disease-related mutations) is well-known in the art.

Also, in order to further clarify the present invention, Applicants have amended Claims 6, 7, 15, 16, 20, 21 and 25 to show that the PTMs are targeting human CFTR pre mRNA.

These arguments are equally applicable to the remaining claims, since in all instances, the PTMs of the invention are directed to a specific target pre-mRNA whose structure is known. Thus, the skilled artisan would be able to readily design a PTM, including particular multiple binding domains, based on the teachings of the present invention.

DOUBLE PATENTING REJECTION

Claims 1-5, 8-14, 17-19, 22-24 and 25 have been rejected for obviousness-type double patenting over claims 1-3 of co-owned U.S. Patent No. 6,013,487. Likewise, Claims 1-26 have been rejected over Claims 1-32 of co-owned U.S. Patent No. 6,280,979. Applicants submit herewith a Terminal Disclaimer to have the terms of a patent granted on the present application be co-extensive with the term of U.S. Patent Nos. 6,013,487 and 6,280,979 to overcome these rejections.

SUBMISSION OF IDS

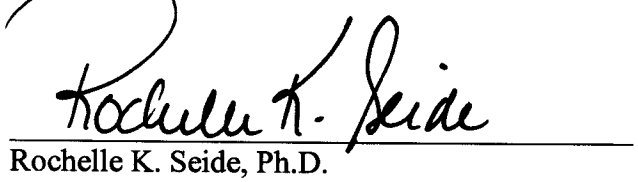
Applicants request that the papers cited above in support of their arguments be made of record in the present application. Applicants also submit an IDS and form PTO 1449 to have the references entered. Applicants request that any fees due for this IDS submission be charged to Deposit Account No. 01-2300.

CONCLUSION

In view of the amendments to the specification and the claims and the Remarks herein, Applicants believe that all of the rejections should be withdrawn and respectfully solicit a Notice of Allowance.

Payment of the extension fee is to be made according to the Credit Card Payment Form attached herewith. Applicants believe that no additional fees are required in connection with this response. However, if additional fees are required, the Commissioner is hereby authorized to charge any additional payment, or credit any overpayment, to Deposit Account No. 01-2300, **referencing Docket Number 027705.00024.**

Respectfully submitted,



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